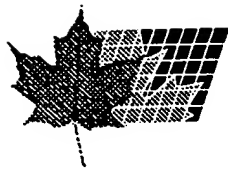


<p>99-132871/12 A96 B05 (B07) MEDE- 97.04.16  MEDEVA PHARM MFG INC *CA 2234282-A  97.04.16 97US-834359 (98.10.16) A61K 31/485, 31/135, 47/06  <b>Drug ion exchange resin complexes stabilised by chelating agents - reduces degradation of solids, gels, or suspensions in storage use for basic, amphoteric and acidic drugs e.g. dextromethorphan</b>  C99-039017  Addnl. Data: EICHMAN M L  98.04.02 98CA-2234282</p>	<p>A(8-A7, 12-V1) B(4-A4, 4-C3B, 10-B1B, 10-B3B, 12-M10) .5</p> <p>dextromethorphan, codeine, morphine, hydrocodone, pseudoephedrine and phenylpropanolamine.</p> <p>Formulations may be for oral, topical, rectal, vaginal, nasal, or ophthalmic administration, as, e.g., a tablet, capsule, powder, lotion, cream, or suppository. Most notable are oral formulations, either immediate or delayed release, in which the latter may have a diffusion barrier or enteric coating.</p>
<p>A pharmaceutical composition in the form of a solid or a gel, comprising a drug-resin complex and a chelating agent, is new.</p> <p><b>USE</b></p> <p>Chelation improves the stability of drugs formulated as resin complexes, reducing degradation and improving storage stability. The resins are notably ion exchange resins, either cationic, e.g. divinylbenzene sulphonic acid (DVBS) or anionic. Drugs formulated in this way include basic, acidic, and amphoteric drugs, having polar groups opposite to the resin i.e. basic drugs with cationic resins and acidic drugs with anionic resins. Many drugs have been found to be more unstable as these resin complexes, either in dry form, or as solutions or suspensions. Specific examples given include</p>	<p><b>PREFERRED COMPOSITION</b></p> <p>Binding of the chelating agent to the resin can be either covalent or non-covalent. Examples of chelating agents are EDTA or its salts, desferrioxamine B, deferoxamine, sodium dithiocarb, penicillamine, calcium or sodium pentetate, succimer, trientine, nitrilotriacetic acid, trans-diaminocyclohexane tetracetic acid, diethylenetriamine pentaacetic acid, bis(aminoethyl)glycol ether N,N,N',N'-tetraacetic acid, iminodiacetic acid, tartaric acid, fumaric acid, or their salts; most notably EDTA or its salts.</p> <p>The concentration of chelating agent is 0.001-10 (preferably 0.1-5) wt.% and should be sufficient to reduce the amount of degradation</p> <p>CA 2234282-A+</p>

<p>of drug in the resin by more than 20 % over a 12 month storage period at room temperature, compared to non-chelated complexes.</p> <p>Preparation of the chelate/drug/resin complex comprises:</p> <p>(a) combining drug and ion exchange resin in a <u>liquid</u> to form a drug resin complex;</p> <p>(b) adding a chelating agent; and</p> <p>(c) drying to a solid or gel.</p> <p>Solvating agents, notably polyethylene glycol (PEG), are optionally added, to reduce particle breaking and aid application of coatings.</p> <p><b>EXAMPLE</b></p> <p>Codeine sulphate (17.6 g) was dissolved in water (700 ml), and DVBS resin Na form (Amberlite IRP 70, RTM, 656 g) added, the whole mixed for 2 hours, and centrifuged to remove the water. Di-Na EDTA (3.6 g) and NaOH (0.8 g) were dissolved in water (170 ml), and PEG 3350 (213 g) added. The solution was added to the drug resin complex suspension, mixed well, and dried on a fluid bed at 25-50 °C to a moisture content of 6-10 %. The EDTA content of the formulation was 0.36%. The formulation was then spray coated with a solution of ethylcellulose 50 cPs 3.4 %, and vegetable oil 1.4 %, in acetone 6.3 % and CH<sub>2</sub>Cl<sub>2</sub> 88.9 %.</p>	<p>In storage stability tests at room temperature, after 6 and 12 months, the codeine contents were 90 % and 94 % of the original, with less than 0.5 % codeinone degradation product present. For a similar formulation without EDTA, the figures were 86 % and 80 % of the original respectively, and codeinone content 2.6 % and 6.0 %. At 37 °C and 6 months, differences were more marked, 89 % of initial and again less than 0.5 % codeinone, for the EDTA formulation, and 58 % with 5.0 % codeinone without EDTA. (RP2) (47pp2259DwgNo.0/0)</p> <p>CA 2234282-A</p>
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USP No. 598 0882

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AN 1999-132871 [12] WPIDS  
DNC C1999-039017  
TI Drug ion exchange resin complexes stabilised by chelating agents -  
reduces  
degradation of solids, gels, or suspensions in storage use for basic,  
amphoteric and acidic drugs e.g. dextromethorphan.  
DC A96 B05 B07  
IN EICHMAN, M L; EICHMAN, M  
PA (MEDE-N) MEDEVA PHARM MFG INC  
CYC 25  
PI CA---2234282 A 19981016 (199912)\* 47p  
EP---911039 A2 19990428 (199921) EN  
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO  
SE SI  
ADT CA---2234282 A 1998CA-2234282 19980402; EP---911039 A2 1998EP-0201125  
19980408  
PRAI 1997US-0834359 19970416



- (72) EICHMAN, Martin L., US  
(71) MEDEVA PHARMACEUTICALS MANUFACTURING, INC., US  
(51) Int.Cl.<sup>6</sup> A61K 31/485, A61K 31/135, A61K 47/06  
(30) 1997/04/16 (08/834,359) US  
(54) **COMPLEXES MEDICAMENT/RESINE STABILISES PAR DES  
CHELATEURS**  
(54) **DRUG-RESIN COMPLEXES STABILIZED BY CHELATING  
AGENTS**

(57) Composition pharmaceutique sous forme solide ou en gelée comprenant un complexe médicament/résine et un chélateur. La présente invention fait également état d'une méthode de fabrication de cette composition et d'une méthode pour améliorer la stabilité d'une composition pharmaceutique.

(57) The invention provides a pharmaceutical composition comprising a drug-resin complex and a chelating agent in which the composition is in the form of a solid or a gel. The invention also provides a method of making such a composition and a method for improving the stability of a pharmaceutical composition.

CA 02234282 1998-04-02

ABSTRACT

The invention provides a pharmaceutical composition comprising a drug-resin complex and a chelating agent in which the composition is in the form of a solid or a gel. The invention also provides a method of making such a composition and a method for improving the stability of a pharmaceutical composition.

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SPECIFICATION

TO ALL WHOM IT MAY CONCERN:

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BE IT KNOWN THAT I, Martin L. Eichman, a resident of Fairport, New York, and a citizen of the United States of America, have invented certain new and useful improvements in

30

**DRUG-RESIN COMPLEXES STABILIZED BY CHELATING  
AGENTS**

of which the following is a specification.

# DRUG-RESIN COMPLEXES STABILIZED BY CHELATING AGENTS

## FIELD OF THE INVENTION

5           The present invention relates generally to pharmaceutical compositions. The invention particularly relates to drug-resin complexes stabilized by chelating agents and a method of making these drug-resin complexes. Another aspect of the invention is a method for using such stabilized drug-resin complexes in the treatment of patients.

10

## BACKGROUND OF THE INVENTION

          The reaction or complexation of a drug with an ion exchange resin forms a composition known as a drug-resin complex. A drug for the purposes of the present invention is a medicinal substance for internal or external use. An ion exchange resin is an ionic, or charged, compound which has binding sites that can bind or take up an ionic drug. The most common types of ion exchange resins are polymers. Such a compound is called a resin because the polymer is formed into very small particles or beads.

20           Drug-resin complexes have several advantages over pure drugs in ordinary formulations. Many drugs are bitter and some smell bad. Getting a patient, particularly a small child or an elderly person, to swallow something that tastes or smells bad can be a serious problem. Complexing such a drug with a resin often improves the taste or the smell.

25           Complexing a drug with a resin can also change its physical characteristics. This change may make the drug more convenient to mass produce or easier for patients to take. For example, mixing a drug in powder form with inert ingredients and compressing the mixture into a tablet is a very common and inexpensive way of preparing a drug for

consumption. However, if a particular drug in liquid or powder form tends to make a crumbly or sticky mixture, large-scale automated tablet compression may be impossible or overly costly. Complexing a drug with a resin can sometimes improve compression characteristics.

5           Complexing a drug with a resin can affect the rate at which the drug dissolves in the digestive system of a patient. Fast dissolution can be a problem if it means the drug has to be taken often to maintain a reasonably even level of the drug in the blood. If a drug causes stomach upset when it dissolves, rapid dissolution in the stomach may also be undesirable.

10          Drug-resin complexes often dissolve more slowly than an ordinary drug formulation. Complexes are useful in changing dissolution profiles and are frequently used in time-release formulations. Coating of a drug-resin complex can delay the release of a drug even more.

            The technique for adsorption of a drug onto an ion exchange resin to  
15          form a drug-resin complex is well-known. Generally the drug is mixed with an aqueous suspension of the ion exchange resin and the complex is dried. Complexation of the drug by the resin may be detected by a change in pH or by other changes in physical properties or by a decrease in concentration of drug dissolved in the aqueous phase.

20           Ion exchange resins are usually made from a polymer backbone with various displaceable functional groups ionically bonded to the polymer. In water the functional groups of the resin ionize. The polymer chains are also typically cross linked, leading to a gel-like insoluble composition formed in beads. The particle size of a resin can differ between two resins  
25          even though the polymer it is made from is the same. The amount of cross linking also varies from one resin to another. The amount of drug which can be bound to a particular resin is called its binding capacity or loading.

Binding capacity varies greatly between resins and from drug to drug. Most resins are sold in dehydrated form and then soaked in water prior to use.

Cationic ion exchange resins have negatively charged, or anionic, binding sites. The anionic binding sites are bonded to displaceable cationic groups. Cationic drugs are positively charged and tend to displace the cationic groups, typically becoming bonded to the resin by ionic bonds. Since basic drugs are generally cationic, cationic exchange resins are often used to prepare drug-resin complexes with basic drugs. Typical approaches to forming a water insoluble drug-resin complex are to react the sodium salt of a cationic ion exchange resin with a cationic drug or to react the base form of the drug with the acid form of the cationic ion exchange resin.

Anionic ion exchange resins have positively charged, or cationic, binding sites. The cationic binding sites are bonded to displaceable anionic groups. Anionic drugs are negatively charged and tend to displace the anionic groups, typically becoming bonded to the resin by ionic bonds. Since acidic drugs are generally anionic, anionic exchange resins are frequently used to prepare drug-resin complexes for acidic drugs. Once a drug-resin complex reaches the digestive system of a patient, the many ions present there tend in turn to displace the drug from the resin and release the drug.

Many drugs have been found to be chemically unstable when reacted with a resin. The drug alone does not degrade in the same way. The decomposition products generally are oxidized forms of the drug, or in some cases hydrolytic products. This decomposition occurs both in the presence of water and when the drug-resin complex is dry. U.S. Patent No. 5,413,782 (Warchol et al.) describes a method for increasing take-up of the drug and preventing decomposition of anionic drug-ion exchange resin



systems. This method involves, not adding a chemical, but rather reacting the drug and the resin in the absence of carbon dioxide and/or bicarbonate ion.

The use of chelating agents to stabilize chemicals and drugs in solution is known. Chelating agents are scavengers for trace amounts of metal ions. Chelation refers to the formation of an unusually stable bond between an organic compound and an ion or other polar group. Most commonly chelation involves a metal ion. The unusual stability of the bond is due to the ability of the organic compound to bind to a central ion at two or more binding sites, often in a ring formation. Compounds which have this ability are known as chelating agents or chelating ligands. The resulting combination of a chelating ligand with a metal ion is referred to as a metal complex. Many reactions, including many oxidation and decomposition reactions, are catalyzed by trace amounts of metallic ions present in solutions. Many drugs can be degraded through oxidation and hydrolytic reactions which are catalyzed by metal ions. The presence of metallic ions can therefore significantly accelerate the degradation of these drugs. Chelating agents are useful in preventing degradation for drugs in solution. EDTA (ethylene diamine tetraacetic acid) and its salts are examples of powerful chelating agents. EDTA is known to stabilize drugs in solution by retarding their oxidation.

U.S. Patent No. 4,973,607 (Stahlbush et al.) describes the use of antioxidants to improve the chemical stability of cationic exchange resins. This differs from the present invention in that only the resin is involved, not a drug-resin complex. U.S. Patent No. 4,221,778 (Raghunathan) describes prolonged release pharmaceutical preparations made of ion exchange resin drug complexes treated with a solvating agent and provided with a diffusion barrier coating.

U.S. Patent No. 5,368,852 (Umemoto et al.) describes prolonged release liquid pharmaceutical preparations of drug-resin complexes coated with ethylcellulose and including a benzoate preservative to reduce bacterial activity. U.S. Patent Nos. 5,182,102 (DeSantis, Jr. et al.) and 5,540,918 (Castillo et al.) describe drug-resin ophthalmic compositions whose resistance to bacterial contamination is improved by the use of antimicrobials. EDTA is disclosed as an antimicrobial in such compositions.

U.S. Patent No. 4,894,239 (Nonomura et al.) discloses preparations that contain drug-resin complexes in which an antioxidant may be added. U.S. Patent No. 5,152,986 (Lange et al.) also discloses preparations that contain drug-resin complexes in which an antioxidant may be added.

U.S. Patent No. 4,448,774 (Clemente et al.) discloses aqueous pharmaceutical solutions that contain a drug, a pharmaceutically acceptable preservative such as sodium benzoate, and a chelating agent such as ethylene diamine tetraacetic acid. None of the patents described above discloses a pharmaceutical composition in the form of a solid or gel that comprises a drug-resin complex and a chelating agent.

## SUMMARY OF THE INVENTION

The invention provides a pharmaceutical composition comprising a drug-resin complex and a chelating agent, in which the composition is in the form of a solid or a gel.

The invention also provides a method of making a pharmaceutical composition comprising: (a) combining a drug and an ion exchange resin in a liquid to form a drug-resin complex; (b) adding a chelating agent; and (c) drying the result of step (b) to form a solid or gel pharmaceutical composition. The invention also provides a pharmaceutical composition prepared by this method.

The invention also provides a method for improving the stability of a pharmaceutical composition that contains a drug-resin complex comprising adding a chelating agent in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex.

5 Additional features and advantages of the invention are set forth in the description which follows and in part will be apparent from the description. The objectives and other advantages of the invention will be realized and attained by the drug-resin complexes stabilized by chelating agents and their uses as particularly pointed out in the written description  
10 and claims.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed.

#### 15 DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method of using chelating agents to stabilize drugs which have been taken up by resins and, in particular, ion exchange resins. The drugs are not in solution, but rather present in the form of a drug-resin complex. The drug may be any of a wide variety of  
20 drugs suitable for the formation of a drug-resin complex and subject to degradation after complexation. The ion exchange resin may be any non-toxic ion exchange resin. The chelating agent may be added during the formation of the complex, after its formation, or at any time during the process. The stabilization is effective either when the complex is dry or  
25 when the complex is suspended in water. The complex may be coated or uncoated as necessary to obtain a desirable dissolution profile. Solvating agents may be used in the process to prevent the resin particles from breaking and to aid in the application of coatings. It should be noted that

resins such as amphoteric resins and other neutral resins may also be used in the practice of the present invention as long as the binding, complexation, or adsorption of the drug into the resin is sufficient.

The stabilization of a drug-resin complex by a chelating agent  
5 involves reacting a resin with a drug to form the drug-resin complex and adding the chelating agent to the complex. These two steps may occur in any order or may be simultaneous. Additional steps may be included in the procedure, such as adding a solvating agent or a coating. These steps may also occur in any order. The complex is dried before use, but it may be  
10 suspended in liquid again later.

The invention also provides a pharmaceutical composition comprising a drug-resin complex and a chelating agent, wherein the composition is in the form of a solid or a gel. Without the chelating agent, the complexed drug would be degraded by oxidation reactions or  
15 hydrolytic reactions catalyzed by metal ions. The drug to be complexed may be chosen because of some undesirable property of the uncomplexed drug, such as unpleasant taste or odor, or poor compression or dissolution characteristics. The drug in the drug-resin complex can be a basic, acidic, or amphoteric drug. The drug can be a basic drug selected from  
20 dextromethorphan, codeine, morphine, hydrocodone, pseudoephedrine, or phenylpropanolamine.

The resin in the drug-resin complex can be a cationic exchange resin. In a preferred embodiment, the resin is a gel type divinylbenzene sulfonic acid cationic exchange resin, and when using this resin the drug is  
25 preferably a basic drug. The resin in the drug-resin complex can be an anionic exchange resin, and when using this type of resin, the drug in the drug-resin complex is preferably an acidic drug.

The chelating agent preferably is selected from EDTA, a salt of EDTA, desferrioxamine B, deferoxamine, dithiocarb sodium, penicillamine, pentetate calcium, a sodium salt of pentetic acid, succimer, trientine, nitrilotriacetic acid, *trans*-diaminocyclohexanetetraacetic acid (DCTA), diethylenetriaminepentaacetic acid, *bis*(aminoethyl)glycolether-N,N,N',N'-tetraacetic acid, iminodiacetic acid, citric acid, tartaric acid, fumaric acid, or a salt thereof. More preferably, the chelating agent is selected from EDTA or a salt of EDTA. Most preferably the chelating agent is disodium edetate, which is contacted with the drug-resin complex in a solution containing sufficient sodium hydroxide to form a significant amount of tetrasodium edetate in solution.

In one embodiment, the chelating agent is not covalently bound to the drug resin complex. In another embodiment, the chelating agent is covalently bound to the drug resin complex. The chelating agent can be present in a concentration of from 0.001 percent to 10 percent by weight, more preferably from 0.1 to 5 percent by weight. Most preferably, the concentration of the chelating agent is about 0.3 to 0.4 percent by weight for a solid dosage form. For a dosage form which is a suspension, the concentration of the chelating agent is most preferably about 0.05% by weight.

The chelating agent preferably is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. The rate of degradation of a drug in a drug-resin complex depends on the particular drug and resin and other factors such as storage temperature. The rate of degradation is preferably as low as possible. In a preferred embodiment, the chelating agent is present in an amount effective to reduce the amount of degradation of the drug in the drug resin complex by more than 20 percent over twelve months of storage at room temperature relative to an otherwise identical pharmaceutical composition without the chelating

agent. For instance, if two samples of a drug-resin complex, one treated with chelating agent and one untreated, each had 20 percent by weight of drug at the beginning of the twelve month period, and the untreated sample had 18 percent by weight of drug after the end of the 12 month period of storage at room temperature, then 2 percent by weight of the drug degraded in the untreated sample. Then preferably, the amount of degradation of the drug in the drug-resin complex treated with chelating agent after the 12 month period of storage at room temperature will be reduced by more than 20 percent, i.e., instead of 2 percent by weight of degradation, less than 1.6 percent by weight of degradation.

The drug-resin complex can comprise a diffusion barrier coating, in a preferred embodiment the diffusion barrier coating is an enteric coating. The diffusion barrier coating improves the dissolution characteristics of the drug-resin complex. The drug-resin complex preferably comprises a solvating agent, and the solvating agent preferably is polyethylene glycol. In a preferred embodiment, the drug-resin complex comprises a solvating agent and a diffusion barrier coating. In another preferred embodiment, the resin in the drug-resin complex is a divinylbenzene sulfonic acid cationic exchange resin, the drug is a basic drug, and the chelating agent is EDTA or a salt of EDTA.

The pharmaceutical composition is suitable for oral, topical, rectal, vaginal, nasal, or ophthalmic administration. The pharmaceutical composition can be in the form of a tablet, a capsule, a powder, a lotion, a cream, or a suppository. In a preferred embodiment, the pharmaceutical composition is suitable for oral administration.

The invention also provides a method of making a pharmaceutical composition comprising: (a) combining a drug and an ion exchange resin in a liquid to form a drug-resin complex; (b) adding a chelating agent; and (c) drying the result of step (b) to form a solid or gel pharmaceutical

composition. Preferably the chelating agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex.

5       The invention also provides a method of making a pharmaceutical composition comprising: (a) combining a drug and an ion exchange resin in a liquid to form a drug-resin complex; (b) adding a chelating agent; (c) drying the result of step (b) to form a solid; and (d) suspending the result of step (c) in an appropriate liquid to form a liquid pharmaceutical composition.

10       The invention provides a method of making a pharmaceutical composition comprising: (a) combining a drug and an ion exchange resin in a first liquid to form a drug-resin complex; (b) drying the result of step (a) to form a solid; (c) suspending the result of step (b) in an appropriate second liquid, which may be the same or different than the first liquid; and  
15       (d) adding a chelating agent, to form a liquid pharmaceutical composition.

      The invention also provides a pharmaceutical composition prepared by the process of: (a) combining a drug and an ion exchange resin in a liquid to form a drug-resin complex; (b) adding a chelating agent; and (c) drying the result of step (b) to form a solid or gel pharmaceutical  
20       composition.

      The invention further provides a pharmaceutical composition prepared by the process of: (a) combining a drug and an ion exchange resin in a liquid to form a drug-resin complex; (b) adding a chelating agent; (c) drying the result of step (b) to form a solid; and (d) suspending the  
25       result of step (c) in an appropriate liquid to form a liquid pharmaceutical composition.

      The invention also provides a pharmaceutical composition prepared by the process of: (a) combining a drug and an ion exchange resin in a first liquid to form a drug-resin complex; (b) drying the result of step (a) to

form a solid; (c) suspending the result of step (b) in an appropriate second liquid, which may be the same or different than the first liquid; and (d) adding a chelating agent, to form a liquid pharmaceutical composition.

The invention provides a method for improving the stability of a pharmaceutical composition that contains a drug-resin complex comprising adding a chelating agent in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. The composition may be a solid, gel, or suspension. The chelating agent preferably is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex by 20 percent over twelve months of storage at room temperature relative to an otherwise identical pharmaceutical composition without the chelating agent. In a preferred embodiment, the agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex by 30 percent over twelve months of storage at room temperature, and in another preferred embodiment, the agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex by 50 percent over twelve months of storage at room temperature.

The invention also provides a method for administering a drug to a patient in need thereof, comprising: (a) providing a pharmaceutical composition that contains a drug-resin complex that contains the drug; (b) adding a chelating agent; (c) storing the combination of step (b); and (d) subsequently administering the combination of step (b) to the patient. The chelating agent preferably is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex.

Many different resins may be successfully used. The ion exchange resin chosen should not be toxic to humans and generally should not have any medicinal effect by itself. Ion exchange resins known to be useful in the present invention are AMBERLITE IRP-69 and AMBERLITE IRP-70



(both available from Rohm & Haas). These two resins are gel type divinylbenzene sulfonic acid cationic exchange resins. IRP-69 and IRP-70 resins are chemically identical but differ in particle size. Both cationic and anionic exchange resins may be used for the invention. Suitable resins for the practice of the invention include functionalized resins derived from divinylbenzenes, trivinylbenzenes, styrenic, methacrylic, methacrylamide, acrylic, acrylamide, carbacrylic, phenol-formaldehyde, polyhydroxy resins, polycarboxylic, carboxyvinyl, cellulosic, and dextran polymer resins. Also suitable for the invention are inorganic ion exchange resins such as zeolite, fuller's earth, peat, lignite, permutite, dolomite, iron oxide hydrate gel, zirconium oxide hydrate gel, and activated carbon. Amphoteric resins, i.e., those derived from the above monomers but containing both anionic and cationic sites in the same polymer may also be used. Zwitterinonic resins may also be used in the practice of the present invention.

When sulfonic acid cationic exchange resins are used, their particle size is typically in the range of about 25 to about 1000  $\mu\text{m}$ . Many of the illustrative examples employ AMBERLITE® IRP-70 resin, a cationic exchange resin which is 100-200 mesh (75-150  $\mu\text{m}$ ) fractured resin particles of AMBERLITE IR-120. The parent resin of AMBERLITE IR-120 and IR-70 is described by the manufacturer as a gel-type divinylbenzene sulfonic acid cationic exchange resin which swells in water with a pH range of 0 to 14.

All drugs which exist in ionic form in a semi-polar or polar solvent, such as water, are potential candidates for use in the present invention. All acidic and basic drugs are suitable. Examples include drugs having basic groups such as amino groups, hydrazino groups, amidino groups, guanidino groups, and heterocyclic groups containing nitrogen. Additional examples include drugs which are carboxylic acids or amides, or which have carbonyl groups or other acidic groups.

A large percentage of the available pharmaceutically active compounds are capable of forming complexes with ion exchange resins. Stabilization of a drug-resin complex by EDTA is known to be effective for the drugs dextromethorphan, codeine, morphine, hydrocodone, and phenylpropanolamine. Stabilization is also effective for pseudoephedrine, dihydrocodeine, salts and derivatives of morphine, methylephedrine, ephedrin, paraamino salicylic acid, acetyl salicylic acid, phentermine, acetaminophen, pilocarpine, metoclopramide, theophylline, and ibuprofen. Other possible drugs for use in the invention include all alpha-adrenergic agonists and blockers; beta-adrenergic agonists and blockers; narcotic and non-narcotic analgesics; anorexics; antiallergics; antiamebics; antianginals; antiasthmatics; antibacterials such as aminoglycosides, carbacephems, carbapenems, cephalosporins, cephamycins, penicillins, polypeptides, tetracyclines, quinolones, and sulfonamides; anticholinergics; antidepressants; antifungals; nonsteroidal anti-inflammatories; antispasmodics; antiulceratives; antivirals; anxiolytics; calcium channel blockers; dopamine receptor agonists and antagonists; narcotic antagonists; protease inhibitors; respiratory stimulants; retroviral protease inhibitors; reverse transcriptase inhibitors; sedatives such as benzodiazepine derivatives; and cerebral, coronary, and peripheral vasodilators. Of course, depending on the  $pK_a$  of the drug, either an anionic or cationic exchange resin will be selected. In some cases an amphoteric resin may be used depending on the physicochemical properties of the drugs, i.e.,  $pK_a$  as well as binding constants.

Suitable examples of the above families of drugs for use in the present invention include the following.

Alpha-adrenergic agonists that can be used include adrafinil, adrenolone, amidephrine, apraclonidine, budralazine, clonidine, cyclopentamine, detomidine, dimetofrine, dipivefrin, ephedrine,

epinephrine, fenoxazoline, guanabenz, guanfacine, hydroxyamphetamine, ibopamine, indanazoline, isometheptene, mephentermine, metaraminol, methoxamine, methylhexanamine, metizoline, midodrine, modafinil, moxonidine, naphazoline, norepinephrine, norfenefrine, octodrine, 5 octopamine, oxymetazoline, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, phenylpropyl-methylamine, pholedrine, propylhexedrine, pseudoephedrine, rilmenidine, synephrine, talipexole, tetrahydrozoline, tiamenidine, tramazoline, tuaminoheptane, tymazoline, tyramine, and xylometazoline.

10       Beta-adrenergic agonists that can be used include albuterol, bambuterol, bitolterol, carbuterol, clenbuterol, clorprenaline, denopamine, dioxethedrine, dopexamine, ephedrine, epinephrine, etafedrine, ethylnorepinephrine, fenoterol, formoterol, hexoprenaline, ibopamine, isoetharine, isoproterenol, mabuterol, metaproterenol, ethoxyphenamine, 15 oxyfedrine, pirbuterol, prenalterol, procaterol, protokylol, reproterol, rimiterol, ritodrine, salmeterol, soterenol, terbutaline, tretoquinol, tulobuterol, and xamoterol.

Alpha-adrenergic blockers that can be used include amosulalol, rotinolol, dapiprazole, doxazosin, ergoloid mesylates, fenspiride, 20 indoramin, labetalol, naftopidil, nicergoline, prazosin, tamsulosin, terazosin, tolazoline, trimazosin, and yohimbine.

Beta-adrenergic blockers that can be used include acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, 25 bunitrolol, bupranolol, butidine hydrochloride, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol,

oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

Narcotic analgesics that can be used include alfentanil,

- 5 benzylmorphine, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, desomorphine, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, ethylmorphine, hydrocodone, hydromorphone, methadone hydrochloride, morphine, morphine hydrochloride, morphine sulfate, nicomorphine, normethadone, normorphine, opium, oxycodone, 10 oxymorphone, phenoperidine, and propiram.

Non-narcotic analgesics that can be used include aceclofenac,

- acetaminophen, acetanilide, acetylsalicylsalicylic acid, aspirin, carbamazepine, dihydroxyaluminum acetylsalicylate, fenoprofen, fluproquazone, ibufenac, indomethacin, ketorolac, magnesium 15 acetylsalicylate, morpholine salicylate, naproxen, phenacetin, phenyl salicylate, salacetamide, salicin, salicylamide, sodium salicylate, and tolfenamic acid.

Anorexics that may be used include aminorex, amphecloral,

- amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, 20 clortermine, cyclexedrine, dextroamphetamine sulfate, diethylpropion, diphemethoxidine, *n*-ethylamphetamine, fenbutrazate, fenfluramine, fenproporex, furfurylmethyl amphetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, 25 phenylpropanolamine hydrochloride, picilorex, and sibutramine.

Antiallergics that may be used include amlexanox, astemizole,

- azelastine, cromolyn, fenpiprane, ibudilast, lodoxamide, nedocromil, oxatomide pemirolast, pentigetide, picumast, repirinast, suplastast tosylate, tazanolast, tranilast, and traxanox.

Antianginals that can be used include acebutolol, alprenolol, amiodarone, amlodipine, arotinolol, atenolol, barnidipine, bepridil, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, carazolol, carteolol, celiprolol, cinepazet maleate, diltiazem, elgodipine, epanolol, felodipine, gallopamil, imolamine, indenolol, isosorbide dinitrate, 5 sradipine, limaprost, mepindolol, metoprolol, molsidomine, nadolol, nicardipine, nicorandil, nifedipine, nifenalol, nilvadipine, nipradilol, nisoldipine, nitroglycerin, oxprenolol, oxyfedrine, ozagrel, penbutolol, pentaerythritol tetranitrate, pindolol, pronethalol, propranolol, ranolazine, 10 somotiadil, sotalol, terodiline, timolol, toliprolol, trolnitrate phosphate, verapamil, and zatebradine.

Antiasthmatics that can be used include amlexanox, azelastine, cromolyn, ibudilast, ketotifen, montelukast, nedocromil, oxatomide, pranlukast, seratrovast, suplatast tosylate, tiaramide, traxanox, zafirlukast, 15 and zileuton.

Antibacterials or antibiotics can be used. The general classes of aminoglycosides, carbacephems, carbapenems, cephalosporins, cephamycins, penicillins, polypeptides, tetracyclines, etc. can be used. Specific antibacterials or antibiotics that can be used include amikacin, 20 dihydrostreptomycin, kanamycin, neomycin, neomycin undecylenate, spectinomycin, streptomycin, loracarbef, biapenem, cefaclor, cefazolin, cefepime, cephalosporin C, cefbuperazone, amdinocillin, amoxicillin, ampicillin, cloxacillin, metampicillin, penicillin G benzathine, penicillin G procaine, penicillin V, piperacillin, amphotomycin, vancomycin, viomycin, 25 apicycline, chlortetracycline, methacycline, and tetracycline.

Synthetic antibacterials such as quinolones and analogs, sulfonamides, etc. can be used. Specific synthetic antibacterials that can be used include cinoxacin, lomefloxacin, nalidixic acid, oxolinic acid, acetyl

sulfa-methoxypyrazine, mafenide, succinylsulfathiazole, sulfacetamide, sulfadiazine, and sulfaloxic acid.

Anticholinergics that can be used include adiphenine hydrochloride, aminopentamide, atropine, chlorphenoxamine, cyclodrine; mecloxamine  
5 pentapiperide, phencarbamide, pridinol, and scopolamine.

Antidepressants that can be used include bicyclics, hydrazides, hydrazines, pyrrolidones, tetracyclics, tricyclics, etc. Specific antidepressants that can be used include binedaline, nefopam, trazodone, iproniazid, rolipram, maprotiline, adinazolam, amitriptyline, clomipramine,  
10 imipramine, nortriptyline, primipramine, adrafinil, milnacipran, nefazodone, and zimeldine.

Synthetic antifungals that can be used include allylamines, imidazoles, thiocarbamates, triazoles, etc. Specific synthetic antifungals that can be used include butenafine, bifonazole, butoconazole,  
15 chlordanoin, clotrimazole, tolciolate, fluconazole, acrisorcin, exalamide, triacetin, and zinc propionate.

Nonsteroidal anti-inflammatories that can be used include aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid  
20 derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, etc. Specific nonsteroidal anti-inflammatories that can be used include flufenamic acid, terofenamate, acetmetacin, clopirac, indomethacin, metiazinic acid, fenbufen, clidanac, alminoprofen, bucloxic acid, ketoprofen, naproxen, tiaprofenic acid, difenamizole, apazone,  
25 mofebutazone, phenylbutazone, acetaminosalol, lysine acetylsalicylate, parsalimide, ampiroxicam, bendazac, nabumetone, superoxide dismutase, and zileuton.

Antispasmodics that can be used include alibendol, ambucetamide, aminopromazine, apoatropine, bevonium methyl sulfate, bietamiverine, butaverine, butropium bromide, caroverine, cimetropium bromide, cinnamedrine, clebopride, cyclonium iodide, difemerine, diisopromine, dioxaphetyl butyrate, diponium bromide, drofenine, emepronium bromide, fenalamide, fenoverine, flavoxate, flopropione, gluconic acid, hydramitrazine, hymecromone, octamylamine, pentapiperide, phloroglucinol, pinaverium bromide, piperilate, prifinium bromide, proxazole, racefimine, rociverine, spasmolytol, sultroponium, tigloidine, tiotropamide, tricromyl, trimebutine, and xenytrpium bromide.

Antiulceratives that can be used include acetoxolone, aldioxa, arbaprostil, benexate hydrochloride, carbenoxolone, cetraxate, cimetidine, colloidal bismuth subcitrate, ebrotidine, ecabet, enprostil, esaprazole, famotidine, gefarnate, guaiazulene, irsogladine, lansoprazole, misoprostol, nizatidine, omeprazole, ornoprostil, pantoprazole, pifarnine, pirenzepine, plaunotol, polaprezinc, rabeprazole, ranitidine, rebamipide, rioprostil, rosaprostol, rotraxate, roxatidine acetate, sofalcone, spizofurone, sucralfate, telenzepine, teprenone, trimoprostil, trithiozine, troxipide, and zolimidine.

Antivirals such as purines, pyrimidines, etc. can be used. Specific antivirals that can be used include acyclovir, cidofivir, cytarabine, dideoxyadenosine, didanosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, inosine pranobex, lamivudine, penciclovir, sorivudine, stavudine, zidovudine, acemannan, amantadine, amidinomyacin, lysozyme, nevirapine, and ribavirin.

Anxiolytics such as arylpiperazines, benzodiazepine derivatives, carbamates, etc. can be used. Specific anxiolytics that can be used include buspirone, lesopitron, alprazolam, bromazepam, diazepam, fludiazepam,

loxapine, metaclazepam, prazepam, cyclobamate, meprobamate, abecarnil, benzocetamine, glutamic acid, mephenoqualone, and pazinaclone.

Calcium channel blockers such as arylalkylamines, dihydropyridine derivatives, piperazine derivatives, etc. can be used. Specific calcium  
5 channel blockers that can be used include bepridil, diltiazem, gallopamil, terodiline, amlodipine, benidipine, lercanidipine, nicardipine, cinnarizine, and fantofarone.

Dopamine receptor agonists can be used. Specific dopamine receptors that can be used include bromocriptine, cabergoline, carmoxirole,  
10 dopexamine, fenoldopam, ibopamine, lisuride, pergolide, pramipexole, quinagolide, ropinirole, roxindole, and talipexole.

Dopamine receptor antagonists can be used. Specific dopamine receptor antagonists that can be used include amisulpride, clebopride, domperidone, metoclopramide, mosapramine, nemonapride, romoxipride, risperidone,  
15 sulpiride, sultopride, and ziprasidone.

Narcotic antagonists can be used. Specific narcotic antagonists that can be used include amiphenazole, cyclazocine, levallorphan, nalmeferine, nalorphine, naloxone, and naltrexone.

Protease inhibitors can be used. Specific protease inhibitors that can  
20 be used include aprotinin, camostat, gabexate, nafamostat, and urinastatin.

Respiratory stimulants can be used. Specific respiratory stimulants that can be used include almitrine, bemegride, cropropamide, crotethamide, dimeflin, dimorpholamine, doxapram, ethamivan, fominoben, lobeline, mepixanox, nikethamide, picrotoxin, pimeclone, pyridofylline, sodium  
25 succinate, and tacrine.

Retroviral protease inhibitors can be used. Specific retroviral protease inhibitors that can be used include indinavir, and ritonavir.

Reverse transcriptase inhibitors can be used. Specific reverse transcriptase inhibitors that can be used include delavirdine, didanosine,



dideoxyadenosine, foscarnet sodium, lamivudine, nevirapine, stavudine, suramin sodium, zalcitabine, and zidovudine.

Sedatives such as benzodiazepine derivatives can be used. Specific sedatives that can be used include brotizolam, cinolazepam, doxefazepam, 5 estazolam, flunitrazepam, flurazepam, haloxazolam, lorazepam, lorazepam, nitrazepam, quazepam, temazepam, and triazolam.

Cerebral vasodilators can be used. Specific cerebral vasodilators that can be used include bencyclane, cinnarizine, citicoline, cyclandelate, ciclonicate, eburnamonine, fasudil, fenoxedil, flunarizine, ibudilast, 10 ifenprodil, lomerizine, nafronyl, nicametate, nicergoline, nimodipine, papaverine, pentifylline, tinofedrine, vincamine, vinpocetine, and viquidil.

Coronary vasodilator can be used. Specific coronary vasodilators that can be used include amotriphene, bendazol, benfurodil hemisuccinate, benziadarone, chloracizine, chromonar, clobenfurol, clonitrate, 15 cloricromen, dilazep, dipyridamole, droprenilamine, efloxate, erythryl tetranitrate, etafenone, fendiline, floredil, ganglefene, heart muscle extract, hexobendine, itramin tosylate, khellin, lidoflazine, mannitol hexanitrate, medibazine, pentaerythritol tetranitrate, pentrinitrol, perhexiline, pimefylline, prenylamine, propatyl nitrate, pyridofylline, trapidil, 20 tricromyl, trimetazidine, trolnitrate phosphate, and visnadine.

Peripheral vasodilator can be used. Specific peripheral vasodilators that can be used include bamethan, bencyclane, betahistine, bradykinin, brovincamine, bufeniode, buflomedil, butalamine, cetiedil, ciclonicate, cinepazide, cyclandelate, eledoisin, fenoxedil, flunarizine, hepronicate, 25 ifenprodil, iloprost, inositol niacinate, isoxsuprine, kallidin, kallikrein, moxisylvyte, nafronyl, nicametate, nicergoline, nicofuranose, nicotiny alcohol, nylidrin, pentifylline, pentoxifylline, piribedil, suloctidil, tolazoline, and xanthinol niacinate.

Antamebics that can be used include arsthinol, bialamicol, carbarsone, cephaeline, chlorbetamide, chloroquine, chlorphenoxamide, chlortetracycline, dehydroemetine, dibromopropamidine, diloxanide, diphetarstone, emetine, fumagillin, glaucarubin, iodoquinol, paromomycin, 5 phanquinone, polybenzarsol, propamidine, quinfamide, secnidazole, sulfarside, teclozan, tetracycline, thiocarbamizine, thiocarbarsone, and tinidazole.

Adsorption of the drug onto the resin particles, i.e., ion exchange resin particles to form the drug resin complex is a well known technique as 10 shown in U.S. Patent Nos. 2,990,332 (Keating) and 4,221,778 (Raghunathan). In general, the drug is mixed with an aqueous suspension of the resin, and the complex is then washed and dried. Adsorption of drug onto the resin may be detected by a change in the pH of the reaction medium or by a reduction in the concentration of dissolved drug in the 15 reaction solvent. Again, the  $pK_a$  of the drug will determine the type of resin which can be used. Generally the loading of the drug on the resin particles can be from about 1 to about 90 percent by weight, although 15 to 50 percent by weight is in the normal practical range.

Several different chelating agents are useful in stabilizing drug-resin 20 complexes. However, the chelating agent is preferably EDTA or one of the salts of EDTA. More than one type of chelating agent may be used with a particular drug-resin complex. The amount of chelating agent should be an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. The appropriate amount of chelating agent easily can be 25 determined by experiment. Salts of EDTA include edetate calcium disodium, edetate trisodium, edetate disodium, and edetate sodium. EDTA and its salts have been found to inhibit the oxidation of drug-resin complexes. Stabilization by EDTA takes place both in the absence of water and when the drug-resin or coated drug-resin is suspended in water.

Other useful chelating agents include desferrioxamine B, deferoxamine, dithiocarb sodium, penicillamine, pentetate calcium, sodium salts of pentetic acid, succimer, trientine, nitrilotriacetic acid, *trans*-diaminocyclohexanetetraacetic acid (DCTA),  
5 diethylenetriaminepentaacetic acid, *bis*(aminoethyl)glycoether-N,N,N',N'-tetraacetic acid, iminodiacetic acid, citric acid, tartaric acid, fumaric acid, or a salt thereof. Preferably the chelating agent is inexpensive and stable, and forms strong metal complexes with a wide variety of metal ions. In addition it is desirable for the chelating agent to be completely non toxic  
10 and to have no pharmacological effect on the body except for its chelating effect. Synthetic multidentate aminocarboxylic acids, such as EDTA, bind metals strongly and are useful chelators for the practice of the invention.

A drug-resin complex is formed by reacting a resin with a drug using standard techniques. For example, a sodium salt of a resin may be  
15 reacted with a cationic drug. The amounts of drug and resin necessary to form an effective drug resin complex will vary greatly. Among the factors to be considered in determining the ratio of drug to resin are the particular drug, the resin used, the reaction conditions, and the final dosage form required. The resin preferably has a high loading capacity for the drug in  
20 question. A small loading capacity may make the resulting dosage form overly bulky or expensive to produce. Actual loading of the drug on the resin particles can range from about 1 to 90 percent by weight but preferably 5 to 30 percent by weight.

Preferably the chelating agent is added after the drug-resin complex  
25 is formed. The drug-resin complex may be dried before adding the chelating agent. EDTA or one of its salts is the preferred chelating agent. Neither resins nor drug-resin complexes are soluble in water, so reactions typically are carried out with the resin in suspension. The chelating agent may be added to the liquid in which the resin is suspended. EDTA

preferably is added to an aqueous suspension of the drug-resin complex. The amount of EDTA should be an amount effective to significantly reduce degradation of the drug-resin complex.

The complex may also be treated by addition of a solvating or  
5 impregnating agent. Possible solvating agents include polyethylene glycol, glycerol, propylene glycol, mannitol, lactose, and methylcellulose. Polyethylene glycol (PEG) is preferred. The solvating agent typically is present in an amount of 5 to 35 parts by weight of the solvating agent to 100 parts by weight of the resin. EDTA most preferably is incorporated  
10 into the resin complex by converting the disodium salt to the tetrasodium salt in an aqueous solution of polyethylene glycol 3350. The EDTA/PEG solution is preferably about 1% EDTA by weight, but may range from about 0.1% to 50%. The amount of sodium hydroxide should be an amount effective to convert the EDTA present to the tetrasodium salt. The  
15 EDTA/PEG solution may be added to a dried drug-resin complex or to an undried complex. The content of EDTA in the drug-resin complex in the final dosage form may vary from about 0.001% to 10% by weight, but is preferably about 0.1 to 0.75% by weight for solid dosage forms and 0.005 to 0.2% by weight for suspensions. The mixture of drug-resin complex,  
20 chelating agent, and solvating agent may be dried to remove all but tightly bound water, or used without drying.

After the drug-resin complex is formed, it may be coated with a film forming polymer. Coating can slow the rate of dissolution and slow absorption of the drug in the gastrointestinal tract. An enteric coating may  
25 be used if it is desirable for the complex to dissolve only in the intestine and not in the stomach. Coatings can be of any film-forming material with diffusion barrier properties. Coatings chosen should not be toxic to humans and generally should not have any pharmacological effect alone. Conventional coating procedures such as those described in U.S. Patent

No. 4,221,778, whose entire contents are incorporated by reference herein, can be used to coat the particles, such as air suspension spray coating or fluid bed spray coating. Coatings generally are applied to the complex, but can be applied to the resin before complexing. Possible coating materials  
5 which can be used include ethylcellulose, methylcellulose, polyethylene glycol, mannitol, lactose and others in solvents such as ethanol, acetone and methylene chloride. EDTA may be added to an aqueous suspension of the coated drug-resin. Varying the amount of coating or combining coated and uncoated complexes in the same formulation can be used to adjust the  
10 dissolution profile as desired. The amount of coating used should be an amount effective to achieve the dissolution characteristics of the drug-resin complex desired for the particular dosage form. Coatings can be used to alter dissolution profiles for syrups, suspensions, suppositories, and capsules as well as for tablets.

15       The effectiveness of stabilization of a given drug-resin complex may be determined by assaying the complex for drug content or activity. The assay results for freshly prepared complex may be compared to results obtained after storage. The addition of the chelating agent to the drug-resin complex significantly improves the stability of the drug in the complex. A  
20 reduction in formation of degradation products is observed.

      The drug-resin complexes of the present invention can be used in pharmaceutical compositions for oral, topical, rectal, vaginal, nasal, or ophthalmic administration. Possible dosage forms include tablets, capsules, powders, syrups, suspensions, lotions, creams, suppositories,  
25 nasal sprays, inhalers, and eye drops, with suspensions being the preferred mode of administration.

      The present invention is further illustrated by the following Examples which are not intended to be limiting. It is to be understood by

those skilled in the art that modifications and changes can be made thereto without departing from the spirit and scope of the invention.

#### EXAMPLE 1

5           Codeine sulfate (17.6 g) was dissolved in 700 mL of water. To the codeine sulfate solution, 656 g of a divinyl benzene sulfonic acid resin, sodium salt (AMBERLITE IRP 70, available from Rohm & Haas) was added and dispersed. The codeine sulfate solution and the resin were mixed for 2 hours, forming a drug-resin complex suspension in an aqueous  
10   vehicle. The resulting mixture was filtered using a screen centrifuge to remove the water.

          Disodium edetate (3.6 g) and 0.8 g of sodium hydroxide were dissolved in 170 mL of water. Polyethylene glycol 3350 (213 g) was added to this solution and dissolved. The sodium hydroxide facilitates the  
15   dissolution of the disodium edetate in the aqueous polyethylene glycol, through formation of the tetrasodium salt of EDTA. The polyethylene glycol solution was added to the drug-resin complex suspension and mixed well. The resulting mixture was dried in a fluid bed dryer by passing warm air through the wet polyethylene glycol treated drug resin complex at a  
20   sufficient velocity to suspend the material being dried. The inlet air temperature was 25 to 50C and the mixture was dried to a moisture content of 6 to 10% by weight. This drying resulted in an EDTA concentration of about 0.36% by weight.

#### EXAMPLE 2

25           A liquid suspension of dextromethorphan polystyrene was prepared in an aqueous vehicle. The aqueous vehicle contained sucrose, high fructose corn syrup, microcrystalline cellulose, carboxymethylcellulose, xanthan gum, orange flavors, methyl and propylparaben, and propylene glycol.

Disodium edetate (0.05% by weight) was added to the suspension and dissolved.

Composition of the Liquid Suspension of Dextromethorphan Polistirex  
Before the Addition of Disodium Edetate

5	Anhydrous Citric Acid	2.0	g
	Propylene Glycol	60.0	g
	Methylparaben	1.5	g
	Propylparaben	0.3	g
	High Fructose Corn Syrup	300.0	g
10	Granulated Sugar	120.0	g
	Polysorbate 80	0.2	g
	Microcrystalline Cellulose and		
	Carboxymethylcellulose Sodium	11.0	g
	Xanthan Gum	1.1	g
15	FD&C Yellow #6	0.023	g
	Orange Flavor	2.0	g
	Purified Water q.s. ad	1.0	L

EXAMPLE 3

20       The dried, EDTA-containing drug resin of Example 1 was coated by spraying a coating solution of ethylcellulose, 50cps, and vegetable oil dissolved in a solvent mixture of acetone and methylene chloride. The composition of coating solution (% by weight) was:

	Ethylcellulose, 50 cps	3.4%
25	Vegetable Oil	1.4%
	Acetone	6.3%
	Methylene Chloride	88.9%

The coating solution was applied by spraying it onto a finely divided powder or granule of the PEG treated drug resin complex in an air

suspension fluid bed processor (Wurster coater). The stability of this coated codeine-resin complex without added EDTA was compared to coated codeine-resin complex with EDTA added. Codeinone is a degradation product of codeine. The area percent of codeinone is therefore an indication of the degradation of the codeine. Codeine and codeinone were quantitated by extracting the resin with a 70% methanol in 1N aqueous ammonium chloride solution and analyzing the extraction solution by HPLC. The percentage of codeinone was estimated by the proportionality of the areas of the codeine and codeinone peaks of the HPLC chromatograms as analyzed spectrophotometrically.

Without EDTA added, after 12 months at room temperature the data showed a decline of 20% in the amount of codeine present. At 37C, the decline was even more marked, 42% less codeine after 6 months. However, with EDTA added, there was a decline of only 4% in the amount of codeine after 25 months at room temperature. At 37C, only 11% less codeine was present after 6 months. The amount of codeinone present was also significantly less with EDTA added.



Stability of Coated Codeine Drug-Resin

<u>Storage Conditions</u>	<u>No EDTA Added</u>			
	<u>Storage Time</u>	<u>% Codeine</u>	<u>/ of Initial % Codeine</u>	<u>% Codeinone</u>
Initial	none	12.2		0.7
RT	3 months	11.2	92	1.4
RT	6 months	10.5	86	2.6
RT	12 months	9.8	80	6.0
37C	3 months	7.5	61	3.7
37C	6 months	7.1	58	5.0
37C	12 months	9.0	74	6.4

Stability of Coated Codeine Drug-Resin

5

<u>EDTA Added</u>				
<u>Storage Conditions</u>	<u>Storage Time</u>	<u>% Codeine</u>	<u>% of Initial % Codeine</u>	<u>% Codeinone</u>
Initial	none	11.8		<0.5
RT	3 months	10.5	89	< 0.5
RT	6 months	10.6	90	<0.5
RT	9 months	10.4	88	<0.5
RT	12 months	11.1	94	< 0.5
RT	25 months	11.3	96	<0.5
37C	3 months	10.8	92	<0.5
37C	6 months	10.5	89	<0.5

#### EXAMPLE 4

The stability of codeine in commercially available PENNTUSS suspension was compared to an experimental PENNTUSS suspension with 0.05% EDTA. Commercial PENNTUSS suspension is an aqueous  
5 suspension containing codeine and chlorpheniramine drug-resin complexes. The experimental suspension contained the EDTA stabilized codeine polistirex from Example 3, plus additional disodium edetate. The total concentration of EDTA in the experimental suspension was 0.05% by weight. The data indicate less decline in codeine content in the suspension  
10 containing EDTA than in the suspension without EDTA. The amount of codeinone present was also generally less in the suspension containing EDTA.

The composition of the experimental suspension was as follows:

	Ingredients	Per Liter
15	Coated Codeine Polistirex	*
	Chlorpheniramine Polistirex	**
	Cleargel Starch	24.2 g
	Xanthan Gum	2.2 g
	Granulated Sugar	100.0 g
20	D & C Red #33	0.025 g
	High Fructose Corn Syrup	300.0 g
	Propylene Glycol	10.0 g
	Methylparaben	1.5 g
	Propylparaben	0.3 g
25	Cherry Cream Flavor	2.86 g
	Polysorbate 80	1.0 g
	Disodium Edetate	0.5 g
	Purified Water q.s. ad	1.0 Liter

\*Equivalent to 2.0 g codeine (base) (15.87 g/L Coated Codeine Polistirex containing 12.6% codeine (base))

\*\*Equivalent to 0.80 g Chlorpheniramine Maleate (2.18 g/L Chlorpheniramine Polistirex containing 25.8% chlorpheniramine (base))

5

The commercial PENTUSS suspension had the same composition as the experimental suspension except that there was no EDTA in the codeine polistirex or in the suspension itself.

10

# Stability of Codeine in Commercial Penntuss Suspension

## No EDTA Added

<u>Package Type</u>	<u>Storage Conditions</u>	<u>Storage Time</u>	<u>Codeine % of Theory</u>	<u>Area % Codeinone</u>
Amber Pint	Initial	none	99.8	2.4
Amber Pint	RT	1 month	98.0	1.7
Amber Pint	RT	3 months	99.4	0.9
Amber Pint	RT	6 months	94.9	1.7
Amber Pint	RT	9 months	99.4	1.6
Amber Pint	RT	12 months	104.3	1.9
Amber Pint	RT	18 months	101.1	1.7
Amber Pint	RT	24 months	97.0	1.0
Amber 3 oz.	Initial	none	101.8	2.1
Amber 3 oz.	RT	1 month	95.0	4.3
Amber 3 oz.	RT	3 months	92.0	Trace
Amber 3 oz.	RT	6 months	95.2	3.5
Amber 3 oz.	RT	9 months	94.3	2.9

Amber 3 oz.	RT	12 months	93.2	4.0
Amber 3 oz.	RT	18 months	88.1	5.7
Amber 3 oz.	RT	24 months	84.9	2.4

Note: ND means not detected.

Stability of Codeine in Experimental Penntuss

0.05% EDTA Added

<u>Package Type</u>	<u>Storage Conditions</u>	<u>Storage Time</u>	<u>Codeine % of Desired</u>	<u>Area % Codeinone</u>
Amber Pint	Initial	none	100.6	0.6
Amber Pint	RT	3 months	100.0	0.6
Amber Pint	RT	6 months	100.8	1.3
Amber Pint	RT	12 months	101.4	<1.0
Amber Pint	Initial	none	98.7	0.6
Amber Pint	RT	3 months	98.7	0.8
Amber Pint	RT	6 months	98.4	1.3
Amber Pint	RT	12 months	99.7	<1.0
Amber 3 oz.	Initial	none	96.4	0.7
Amber 3 oz.	RT	3 months	97.8	0.9
Amber 3 oz.	RT	6 months	98.8	1.6
Amber 3 oz.	RT	12 months	95.5	1.2

5 Note: The package types are types of glass bottles.

### EXAMPLE 5

The stability of dextromethorphan polystyrene drug-resin suspensions with and without 0.05 % disodium edetate by weight was compared. The desired amount was 30 mg dextromethorphan per 5 mL of suspension. The data indicated that without EDTA, the dextromethorphan content declined 10% in 18 months. With EDTA present, there was no decline in dextromethorphan content over 18 months. The dextromethorphan polystyrene drug-resin suspensions tested in the table below were made by preparing coated dextromethorphan polystyrene and suspending the coated dextromethorphan polystyrene in a sufficient quantity of water so that there were 30 mg dextromethorphan per 5 mL of suspension.

Uncoated dextromethorphan polystyrene was prepared by reacting 381.7 g of dextromethorphan hydrochloride with 673 g of AMBERLITE IRP-70, sodium cycle resin, in 4.2 L of purified water for 4 hours and subsequently filtering the reacted dextromethorphan polystyrene using a basket centrifuge. The filtered resin was then dried in a fluid bed dryer.

Coated dextromethorphan polystyrene was prepared by reacting 381.7 g of dextromethorphan hydrochloride with 673 g of AMBERLITE IRP-70, sodium cycle resin, in 4.2 L of purified water for 4 hours and subsequently filtering the reacted dextromethorphan polystyrene using a basket centrifuge. The dextromethorphan polystyrene was then mixed with a solution of 227 g of polyethylene glycol 3350 dissolved in 360 ml of purified water. This mixture was then dried in a fluid bed dryer. The dried material was then milled through a Comil grinder and coated with the same ethylcellulose coating solution as described in Example 3.

The dextromethorphan drug-resin suspensions tested in the table below contained a mixture of coated and uncoated dextromethorphan drug-resin. The ratio of coated to uncoated drug-resin does not affect the rate of degradation of the drug. The ratio of coated to uncoated drug-resin

in the examples below was approximately 2:1 coated/uncoated. However, the range of coated/uncoated drug-resin can range from 9:1 to 1:9.

Dextromethorphan ketone, (-)-3-methyl-10-oxy-methylmorphinan, is a degradation product of dextromethorphan. Dextromethorphan and dextromethorphan ketone were quantitated by separating the resin from the suspension by filtration on a fritted glass funnel and then extracting the resin with a 70% methanol in 1N aqueous ammonium chloride solution and analyzing the extraction solution by HPLC. The percentage of dextromethorphan ketone was estimated by the proportionality of the areas of the dextromethorphan and dextromethorphan ketone peaks of the HPLC chromatograms as analyzed spectrophotometrically.

#### Stability of Dextromethorphan Drug-Resin Suspensions

<u>Storage Conditions</u>	<u>Storage Time</u>	Dextromethorphan	
		Dextromethorphan	% of Desired
		% of Desired	0.05% EDTA
		<u>No EDTA Added</u>	<u>Added</u>
	Initial	102	104
RT	3 months	93	102
RT	6 months	96	105
RT	9 months	89	103
RT	12 months	94	101
RT	18 months	92	104

The above description is provided for the purpose of describing embodiments of the invention and is not intended to limit the scope of the invention in any way. It will be apparent to those skilled in the art that various modifications and variations can be made in the drug-resin complexes stabilized by chelating agents, their methods of manufacture, and their uses without departing from the spirit or scope of the invention.

Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A pharmaceutical composition comprising a drug-resin complex and a chelating agent, wherein the composition is in the form of a solid or a gel.

2. A pharmaceutical composition according to claim 1, wherein the composition is in the form of a solid.

3. A pharmaceutical composition according to claim 1, wherein the drug in the drug-resin complex is a basic drug.

4. A pharmaceutical composition according to claim 1, wherein the drug in the drug-resin complex is an acidic drug.

5. A pharmaceutical composition according to claim 1, wherein the drug in the drug-resin complex is an amphoteric drug.

6. A pharmaceutical composition according to claim 3, wherein the basic drug is selected from dextromethorphan, codeine, morphine, hydrocodone, pseudoephedrine, or phenylpropanolamine.

7. A pharmaceutical composition according to claim 1, wherein the resin in the drug-resin complex is a cationic exchange resin.

8. A pharmaceutical composition according to claim 7, wherein the resin is a divinylbenzene sulfonic acid cationic exchange resin.



9. A pharmaceutical composition according to claim 8, wherein the drug in the drug-resin complex is a basic drug.

10. A pharmaceutical composition according to claim 1, wherein the resin in the drug-resin complex is an anionic exchange resin.

11. A pharmaceutical composition according to claim 10, wherein the drug in the drug-resin complex is an acidic drug.

12. A pharmaceutical composition according to claim 1, wherein the chelating agent is selected from EDTA, a salt of EDTA, desferrioxamine B, deferoxamine, dithiocarb sodium, penicillamine, pentetate calcium, a sodium salt of pentetic acid, succimer, trientine, nitrilotriacetic acid, *trans*-diaminocyclohexanetetraacetic acid (DCTA), diethylenetriaminepentaacetic acid, *bis*(aminoethyl)glycoether-N,N,N',N'-tetraacetic acid, iminodiacetic acid, acetic acid, tartaric acid, fumaric acid, or a salt thereof.

13. A pharmaceutical composition according to claim 1, wherein the chelating agent is selected from EDTA or a salt of EDTA.

14. A pharmaceutical composition according to claim 1, wherein the chelating agent is not covalently bound to the drug resin complex.

15. A pharmaceutical composition according to claim 1, wherein the chelating agent is covalently bound to the drug resin complex.

16. A pharmaceutical composition according to claim 14, wherein the chelating agent is selected from EDTA or a salt of EDTA.

17. A pharmaceutical composition according to claim 1, wherein the chelating agent is present in a concentration of from 0.001 to 10 percent by weight.

5

18. A pharmaceutical composition according to claim 1, wherein the chelating agent is present in a concentration of from 0.1 to 5 percent by weight.

10 19. A pharmaceutical composition according to claim 1, wherein the chelating agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex.

20. A pharmaceutical composition according to claim 19,  
15 wherein the chelating agent is present in an amount effective to reduce the amount of degradation of the drug in the drug resin complex by more than 20 percent over twelve months of storage at room temperature relative to an otherwise identical pharmaceutical composition without the chelating agent.

20

21. A pharmaceutical composition according to claim 1, wherein the drug-resin complex comprises a diffusion barrier coating.

22. A pharmaceutical composition according to claim 21,  
25 wherein the diffusion barrier coating is an enteric coating.

23. A pharmaceutical composition according to claim 1, wherein the drug-resin complex comprises a solvating agent.

24. A pharmaceutical composition according to claim 23, wherein the solvating agent is polyethylene glycol.

25. A pharmaceutical composition according to claim 1, wherein  
5 the drug-resin complex comprises a solvating agent and a diffusion barrier coating.

26. A pharmaceutical composition according to claim 1, wherein  
10 the resin in the drug-resin complex is a gel type divinylbenzene sulfonic acid cationic exchange resin, the drug is a basic drug, and the chelating agent is EDTA or a salt of EDTA.

27. A pharmaceutical composition according to claim 1, wherein  
15 the pharmaceutical composition is suitable for oral, topical, rectal, vaginal, nasal, or ophthalmic administration.

28. A pharmaceutical composition according to claim 1, wherein  
the pharmaceutical composition is in the form of a tablet, a capsule, a powder, a lotion, a cream, or a suppository.  
20

29. A pharmaceutical composition according to claim 27,  
wherein the pharmaceutical composition is suitable for oral administration.

30. A method of making a pharmaceutical composition  
25 comprising:

(a) combining a drug and an ion exchange resin in a liquid to form a drug-resin complex;

(b) adding a chelating agent; and  
(c) drying the result of step (b) to form a solid or gel  
pharmaceutical composition.

5           31. A method according to claim 30, wherein the drug in the  
drug-resin complex is selected from dextromethorphan, codeine, morphine,  
hydrocodone, pseudoephedrine, or phenylpropanolamine.

10           32. A method according to claim 30, wherein the chelating agent  
is selected from EDTA, a salt of EDTA, desferrioxamine B, deferoxamine,  
dithiocarb sodium, penicillamine, pentetate calcium, a sodium salt of  
pentetic acid, succimer, trientine, nitrilotriacetic acid, *trans*-  
diaminocyclohexanetetraacetic acid (DCTA),  
diethylenetriaminepentaacetic acid, *bis*(aminoethyl)glycoether-N,N,N',N'-  
15 tetraacetic acid, iminodiacetic acid, acetic acid, tartaric acid, fumaric acid,  
or a salt thereof.

20           33. A method according to claim 30, wherein the chelating agent  
is selected from EDTA or a salt of EDTA.

            34. A method according to claim 30, wherein the chelating agent  
is present in an amount effective to reduce the rate of degradation of the  
drug in the drug-resin complex.

25           35. A method of making a pharmaceutical composition  
comprising:

(a) combining a drug and an ion exchange resin in a liquid to  
form a drug-resin complex;

(b) adding a chelating agent;

- (c) drying the result of step (b) to form a solid; and
- (d) suspending the result of step (c) in an appropriate liquid to form a liquid pharmaceutical composition.

5           36. A method according to claim 35, wherein the drug in the drug-resin complex is selected from dextromethorphan, codeine, morphine, hydrocodone, pseudoephedrine, or phenylpropanolamine.

10           37. A method according to claim 35, wherein the chelating agent is selected from EDTA, a salt of EDTA, desferrioxamine B, deferoxamine, dithiocarb sodium, penicillamine, pentetate calcium, a sodium salt of pentetic acid, succimer, trientine, nitrilotriacetic acid, *trans*-diaminocyclohexanetetraacetic acid (DCTA), diethylenetriaminepentaacetic acid, *bis*(aminoethyl)glycoether-N,N,N',N'-tetraacetic acid, iminodiacetic acid, acetic acid, tartaric acid, fumaric acid, 15 or a salt thereof.

          38. A method according to claim 35, wherein the chelating agent is selected from EDTA or a salt of EDTA.

20

          39. A method according to claim 35, wherein the chelating agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex.

25           40. A method of making a pharmaceutical composition comprising:

- (a) combining a drug and an ion exchange resin in a first liquid to form a drug-resin complex;
- (b) drying the result of step (a) to form a solid;

- (c) suspending the result of step (b) in an appropriate second liquid, which may be the same or different than the first liquid; and
- (d) adding a chelating agent, to form a liquid pharmaceutical composition.

5

41. A method according to claim 40, wherein the drug in the drug-resin complex is selected from dextromethorphan, codeine, morphine, hydrocodone, pseudoephedrine, or phenylpropanolamine.

10

42. A method according to claim 40, wherein the chelating agent is selected from EDTA, a salt of EDTA, desferrioxamine B, deferoxamine, dithiocarb sodium, penicillamine, pentetate calcium, a sodium salt of pentetic acid, succimer, trientine, nitrilotriacetic acid, *trans*-diaminocyclohexanetetraacetic acid (DCTA),

15

diethylenetriaminepentaacetic acid, *bis*(aminoethyl)glycolether-N,N,N',N'-tetraacetic acid, iminodiacetic acid, acetic acid, tartaric acid, fumaric acid, or a salt thereof.

20

43. A method according to claim 40, wherein the chelating agent is selected from EDTA or a salt of EDTA.

25

44. A method according to claim 40, wherein the chelating agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex.

45. A pharmaceutical composition prepared by the process of:  
(a) combining a drug and an ion exchange resin in a liquid to form a drug-resin complex;

(b) adding a chelating agent; and  
(c) drying the result of step (b) to form a solid or gel  
pharmaceutical composition.

5           46. A pharmaceutical composition prepared by the process of:  
            (a) combining a drug and an ion exchange resin in a liquid to  
form a drug-resin complex;

            (b) adding a chelating agent;  
            (c) drying the result of step (b) to form a solid; and  
10          (d) suspending the result of step (c) in an appropriate liquid to  
form a liquid pharmaceutical composition.

            47. A pharmaceutical composition prepared by the process of:  
            (a) combining a drug and an ion exchange resin in a first liquid  
15 to form a drug-resin complex;

            (b) drying the result of step (a) to form a solid;  
            (c) suspending the result of step (b) in an appropriate second  
liquid, which may be the same or different than the first liquid; and  
            (d) adding a chelating agent, to form a liquid pharmaceutical  
20 composition.

            48. A method for improving the stability of a pharmaceutical  
composition that contains a drug-resin complex comprising adding a  
chelating agent in an amount effective to reduce the rate of degradation of  
25 the drug in the drug-resin complex.

            49. A method according to claim 48, wherein the composition is  
a solid.

50. A method according to claim 48, wherein the composition is a gel.

51. A method according to claim 48, wherein the composition is a suspension.

52. A method according to claim 48, wherein the chelating agent is selected from EDTA, a salt of EDTA, desferrioxamine B, deferoxamine, dithiocarb sodium, penicillamine, pentetate calcium, a sodium salt of pentetic acid, succimer, trientine, nitrilotriacetic acid, *trans*-diaminocyclohexanetetraacetic acid (DCTA), diethylenetriaminepentaacetic acid, *bis*(aminoethyl)glycoether-N,N,N',N'-tetraacetic acid, iminodiacetic acid, acetic acid, tartaric acid, fumaric acid, or a salt thereof.

15

53. A method according to claim 48, wherein the chelating agent is selected from EDTA or a salt of EDTA.

54. A method according to claim 48, wherein the chelating agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex by more than 20 percent over twelve months of storage at room temperature relative to an otherwise identical pharmaceutical composition without the chelating agent.

55. A method for administering a drug to a patient in need thereof, comprising:

(a) providing a pharmaceutical composition that contains a drug-resin complex that contains the drug;

(b) adding a chelating agent;



- (c) storing the combination of step (b); and
- (d) subsequently administering the combination of step (b) to the patient.

5            56. A method according to claim 55, wherein the chelating agent is present in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex.

Smart & Biggar  
Ottawa, Canada  
Patent Agents